WHAT IS CLAIMED IS:

1. A method for introducing one or more mutations into a template double-stranded polynucleotide, wherein the template double-stranded polynucleotide has been cleaved into double-stranded random fragments of a desired size, comprising:

a) adding to the resultant population of double-stranded fragments one or more single or double-stranded oligonucleotides, wherein said oligonucleotides comprise an area of identity and an area of heterology to the template polynucleotide;

b) denaturing the resultant mixture of double-stranded random fragments and oligonucleotides into single-stranded fragments;

c) incubating the resultant population of single-stranded fragments with a polymerase under conditions which result in the annealing of said single-stranded fragments at regions of identity between the single-stranded fragments and formation of a mutagenized double-stranded polynucleotide; and

d) repeating steps (b) and (c).

2. The method of Claim 1 wherein the concentration of a specific double-stranded fragment in the mixture of double-stranded fragments is less than 1% by weight of the total DNA.

3. The method of Claim 1 wherein the number of different specific double-stranded fragments comprises at least about 100.

4. The method of Claim 1 wherein the size of the double-stranded fragments is from about 5 bp to 5 kb.

5. The method of Claim 1 wherein the size of the mutagenized double-stranded polynucleotide comprises from 50 bp to 100 kb.

6. A method of producing recombinant proteins having biological activity comprising:

a) treating a sample comprising double-stranded template polynucleotides encoding a wild-type protein under conditions which provide for the cleavage of said template polynucleotides

into random double-stranded fragments having a desired size;

b) adding to the resultant population of random fragments one or more single or double-stranded oligonucleotides, wherein said oligonucleotides comprise areas of identity and areas of heterology to the template polynucleotide;

c) denaturing the resultant mixture of double-stranded random fragments and oligonucleotides into single-stranded fragments;

d) incubating the resultant population of single-stranded fragments with a polymerase under conditions which result in the annealing of said single-stranded fragments at the areas of identity and formation of a mutagenized double-stranded polynucleotide;

e) repeating steps (c) and (d); and

f) expressing the recombinant protein from the mutagenized double-stranded polynucleotide.

7. The method of Claim 6 wherein the concentration of a specific double-stranded fragment in the mixture of double-stranded fragments in step (a) is less than 1% by weight of the total DNA.

8. The method of Claim 6 where the number of different specific double-stranded fragments in step (a) comprises at least about 100.

9. The method of Claim 6 wherein the size of the double-stranded fragments is from about 5 bp to 5 kb.

10. The method of Claim 6 wherein the size of the mutagenized double-stranded polynucleotide comprises from 50 bp to 100 kb.

11. The method of Claim 6 further comprising selecting the desired recombinant protein from the population of recombinant proteins.

12. A method for obtaining a chimeric polynucleotide comprising:

a) treating a sample comprising different double-stranded

template polynucleotides wherein said different template polynucleotides contain areas of identity and areas of heterology under conditions which provide for the cleavage of said template polynucleotides into random double-stranded fragments of a desired size;

b) denaturing the resultant random double-stranded template fragments contained in the treated sample produced by step (a) into single-stranded fragments;

c) incubating the resultant single-stranded fragments with polymerase under conditions which provide for the annealing of the target single-stranded fragments at the areas of identity and the formation of a chimeric double-stranded polynucleotide sequence comprising template polynucleotide sequences; and

d) repeating steps (b) and (c) as desired.

13. The method of Claim 12 wherein the concentration of a specific double-stranded fragment in the mixture of double-stranded fragments in step (a) is less than 1% by weight of the total DNA.

14. The method of Claim 12 where the number of different specific double-stranded fragments in step (a) comprises at least about 100.

15. The method of Claim 12 wherein the size of the double-stranded fragments is from about 5 bp to 5 kb.

16. The method of Claim 12 wherein the size of the mutagenized double-stranded polynucleotide comprises from 50 bp to 100 kb.

17. A method of replicating a template polynucleotide which method comprises combining *in vitro* single-stranded template polynucleotides with small random single-stranded fragments resulting from the cleavage and denaturation of the template polynucleotide, and incubating said mixture of nucleic acid fragments in the presence of a nucleic acid polymerase under conditions wherein a population of double-stranded template polynucleotides is formed.

18. A method for generating libraries of displayed peptides or displayed antibodies suitable for affinity interaction screening or phenotypic screening, the method comprising:

(1) obtaining a first plurality of selected library members comprising a displayed peptide or displayed antibody and an associated polynucleotide encoding said displayed peptide or displayed antibody, and obtaining said associated polynucleotides or copies thereof wherein said associated polynucleotides comprise a region of substantially identical sequence, and

(2) pooling and fragmenting said associated polynucleotides or copies to form fragments thereof under conditions suitable for PCR amplification, performing PCR amplification, and thereby homologously recombining said fragments to form a shuffled pool of recombined polynucleotides, whereby a substantial fraction of the recombined polynucleotides of said shuffled pool are not present in the first plurality of selected library members.

19. The method of claim 18, further comprising introducing mutations into said polynucleotides or copies.

20. The method of claim 19, wherein the mutations are introduced by performing PCR amplification.

21. The method of claim 20, wherein the PCR amplification is error-prone PCR.

22. The method of claim 18, comprising the additional step of screening the library members of the shuffled pool to identify individual shuffled library members having the ability to bind with a predetermined macromolecule.

23. The method of claim 18, wherein the first plurality of selected library members is obtained by selecting for a phenotypic characteristic other than binding affinity for a predetermined molecule.

24. The method of claim 18, wherein the first plurality of selected library members is pooled and fragmented and

homologously recombined by PCR in vitro.

25. The method of claim 18, wherein the first plurality of selected library members is pooled and fragmented in vitro, the resultant fragments transferred into a host cell or organism and homologously recombined to form shuffled library members in vivo.

26. The method of claim 18, wherein the first plurality of selected library members is cloned or amplified on episomally replicable vectors, a multiplicity of said vectors is transferred into a cell and homologously recombined to form shuffled library members in vivo.

27. A method for generating libraries of displayed peptides or displayed antibodies suitable for affinity interaction screening or phenotypic screening, the method comprising:

(1) obtaining a first plurality of selected library members comprising a displayed peptide or displayed antibody and an associated polynucleotide encoding said displayed peptide or displayed antibody, and obtaining said associated polynucleotides or copies thereof wherein said associated polynucleotides comprise a region of substantially identical sequence, and

(2) cloning or amplifying said associated polynucleotides or copies on episomally replicable vectors and transferring a multiplicity of said vectors into a cell and homologously recombined to form shuffled library members in vivo.

28. The method of claim 27, further comprising introducing mutations into said polynucleotides or copies thereof.

29. The method of claim 27, wherein said episomally replicable vectors comprise a direct repeat of a plurality of associated polynucleotides or copies thereof.

30. A method for generating libraries of displayed antibodies suitable for affinity interaction screening, the method comprising:

(1) obtaining a first plurality of selected library members

comprising a displayed antibody and an associated polynucleotide encoding said displayed antibody, and obtaining said associated polynucleotides or copies thereof, wherein said associated polynucleotides comprise a region of substantially identical variable region framework sequence, and

(2) pooling and fragmenting said associated polynucleotides or copies to form fragments thereof under conditions suitable for PCR amplification, performing PCR amplification, and thereby homologously recombining said fragments to form a shuffled pool of recombined polynucleotides comprising novel combinations of CDRs, whereby a substantial fraction of the recombined polynucleotides of said shuffled pool comprise CDR combinations are not present in the first plurality of selected library members.

31. The method of claim 30, comprising the additional step wherein the shuffled pool is subjected to affinity screening to select shuffled library members which bind to a predetermined epitope and thereby selecting a plurality of selected shuffled library members.

32. The method of claim 31, comprising the additional step of shuffling the plurality of selected shuffled library members and screening, from 1 to about 1000 cycles.